PRD2008-08

Proposed Registration Decision

Fluazinam

(publié aussi en français)

28 May 2008

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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ISBN: 978-0-662-48856-9 (978-0-662-48857-6)
Catalogue number: H113-9/2008-8E (H113-9/2008-8E-PDF)

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Overview

Proposed Registration Decision for Fluazinam

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing conversion from conditional to full registration for the sale and use of Technical Fluazinam Fungicide and Allegro 500F Agricultural Fungicide containing the technical grade active ingredient fluazinam to control late blight on potatoes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Technical Fluazinam Fungicide (Pest Control Product Registration Number 27516) and Allegro 500F Agricultural Fungicide (Pest Control Product Registration Number 27517) are currently conditionally registered in Canada for ground application. The detailed review of these products can be found under Regulatory Note REG2003-12, *Fluazinam*. The purpose of the current applications are to convert Technical Fluazinam Fungicide and Allegro 500F Agricultural Fungicide from conditional registration to full registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Technical Fluazinam Fungicide and Allegro 500F Agricultural Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

Before making a final registration decision on fluazinam, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on fluazinam, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Fluazinam?

Fluazinam is the active ingredient in Allegro 500F Agricultural Fungicide. This preventative fungicide is a contact fungicide that acts on the surface of the plant to control late blight on potatoes.

Health Considerations

Can Approved Uses of Fluazinam Affect Human Health?

Fluazinam is unlikely to affect your health when used according to the label directions.

Exposure to fluazinam may occur through diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human populations (e.g. children and nursing mothers).

Only those uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

much higher) than levels to which humans are normally exposed when using fluazinam products according to label directions.

Fluazinam caused thyroid tumours in male rats and liver tumours in male mice. However, these tumour types seen in the respective rodents studied are rarely seen in the general human population. There was also no indication that fluazinam caused damage to the nervous system. The first signs of toxicity in animals given daily doses of fluazinam over longer periods of time were effects on body weight, liver, uterus and blood chemistry. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When fluazinam was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, though the effects observed were more severe, indicating the fetus was more sensitive to fluazinam than the adult animal. Also, potentially endocrine-related effects were seen in the two year mouse study. Consequently, extra protective measures were applied during the risk assessment to further reduce the allowable level of human exposure to fluazinam.

Residues in Water and Food

Dietary risks from food and water are not of concern

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Dietary intake estimates (food plus water) revealed that children and adults including seniors will typically consume less than 2% of the acceptable daily intake for fluazinam. Infants, the segment of the population that would ingest the most fluazinam relative to body weight, are expected to be exposed to less than 2% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from fluazinam is not a concern for all population subgroups.

New animal studies resulted in revisions to the acute toxicological endpoints. The aggregate (food and water) dietary intake estimate, based on these revised endpoints, for females of childbearing age (13 to 49 years old) and the total population (including infants and children) were each less than 7% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the

maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The residue trials submitted to support the registration of Allegro 500F Agricultural Fungicide on potatoes were conducted throughout Canada and the United States using end-use products containing fluazinam. These trials were sufficient to propose an MRL for potatoes and processed food derived from potatoes. This MRL can be found in the Science Evaluation of this Proposed Registration Decision.

Occupational Risks From Handling Fluazinam

Occupational risks are not of concern when Allegro 500F Agricultural Fungicide is used according to the label directions, which include protective measures.

The label will specify that anyone mixing, loading or applying Allegro 500F Agricultural Fungicide or performing clean-up or repair activities must wear coveralls over long-sleeved shirt and long pants, shoes plus socks and chemical-resistant gloves. Taking into consideration these label requirements, the risk to workers handling Allegro 500F Agricultural Fungicide is not of concern.

Environmental Considerations

What Happens When Fluazinam Is Introduced Into the Environment?

Fluazinam presents a risk to freshwater and marine aquatic organisms. It also poses dietary and reproductive risk to wild mammals. Therefore, buffer zones are required to protect sensitive aquatic habitats when fluazinam is applied. In addition, an environmental hazard statement based on the persistence and high carryover of fluazinam must be added to the label of the end-use product, Allegro 500F, to protect sensitive organisms.

Fluazinam enters the environment when used as a fungicide on potatoes. Fluazinam is moderately persistent in soil. Both fluazinam and the metabolite HYPA are expected to significantly carryover into the next field season. Although the use pattern of fluazinam does not include direct application to bodies of water, the possibility that aquatic systems may be exposed to fluazinam, directly or indirectly, cannot be ruled out. Although fluazinam does not persist in aquatic systems, its major transformation product, CAPA, is stable to hydrolysis in the aquatic environment.

Laboratory and field studies indicate that fluazinam and its major transformation products will not leach through the soil.

Based on its low vapour pressure and Henry's law constant, fluazinam is considered to be non-volatile in the environment. Fluazinam residues are, therefore, not expected in the air and long-range transport is not expected.

Fluazinam presents a negligible risk to earthworms, honeybees, wild birds, sediment dwelling organisms and marine/estuarine fish. Fluazinam is expected to adversely affect the vegetative vigour of terrestrial vascular plants, the dietary and reproductive capacity of wild mammals, freshwater invertebrates (acute and chronic basis), freshwater fish (acute, chronic and reproductive basis), freshwater algae and aquatic vascular plants (acute basis) and marine invertebrates. Therefore, buffer zones and environmental hazard statements on the toxicity of fluazinam to both aquatic and terrestrial organisms were placed on the product label.

Value Considerations

What Is the Value of Allegro 500F Agricultural Fungicide?

Allegro 500F Agricultural Fungicide provides effective control of potato late blight (*Phytophthora infestans*) when applied at 200 g a.i./ha, in 200–600 litres of water per hectare and applied at 7- to 10-day intervals. The level of disease control is similar to other commercial standards that are currently registered for this disease.

The value in registering Allegro 500F Agricultural Fungicide is that it provides Canadian potato growers with an alternative product to control potato late blight. It can be applied up to 10 times throughout the growing season, which may be necessary for season-long control of this disease as late blight can occur at any time during crop production. Allegro 500F Agricultural Fungicide is a Group 29 fungicide containing the active ingredient fluazinam, which has been identified as having a low risk of leading to resistance development. The use of Allegro 500F Agricultural Fungicide will give potato growers a new product with a different mode of action that can be used in rotation with existing chemical control methods and may replace applications of older fungicide chemistries.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of Allegro 500F Agricultural Fungicide to address the potential risks identified in this assessment are as follows.

Human Health

- As there is a concern with users coming into direct contact with fluazinam or Allegro 500F Agricultural Fungicide, hazard statements have been added to the product label to communicate potential hazards to the users.

- Anyone mixing, loading or applying Allegro 500F Agricultural Fungicide or performing clean-up or repair activities must wear coveralls over a long-sleeved shirt and long pants, shoes plus socks and chemical-resistant gloves.

Environment

The following statement must be included on the Allegro 500F Agricultural Fungicide label.

> DO NOT apply during periods of dead calm or when winds are gusty. DO NOT overspray non-target terrestrial or aquatic habitats. DO NOT contaminate aquatic habitats when cleaning and rinsing spray equipment or containers.

Next Steps

Before making a final registration decision on fluazinam, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

At the time the PMRA makes its registration decision, it will publish a Registration Decision on fluazinam (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Fluazinam

1.0 The Technical Grade Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Common Name: Fluazinam

IUPAC Chemical Name: 2-chloro-N-(3-chloro-5-trifluoromethyl-2-pyridyl)-α,α,α-trifluoro-2,6-dinitro-p-toluidine

CAS Chemical Name: 3-chloro-N-[3-chloro-2,6-dinitro-4-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2-pyridinamine

1.2 Physical and Chemical Properties of the Active Ingredient

Technical Product—Technical Fluazinam Fungicide

Property	Result
Colour and physical state	Mustard yellow, solid granular powder
Nominal concentration	97.47%
Odour	Strong musty odour
Density	1.76 g/cm^3
Vapour pressure	2.3×10^{-5} Pa at 25°C
pH	Average pH under ambient conditions = 6.03
Solubility in water	**pH** **Solubility (mg/L)** 5 0.131 7 0.157 9 3.384
n-Octanol–water partition coefficient (log K_{ow})	pH = 7.0 Mean $K_{ow} = 1.08 \times 10^4$ Mean log $K_{ow} = 4.06$

The chemistry requirements for Technical Fluazinam Fungicide are complete.

A detailed assessment of the product chemistry of Technical Fluazinam Fungicide and the end-use product Allegro 500F Agricultural Fungicide are presented in Regulatory Note REG2003-12, *Fluazinam*.

2.0 Methods of Analysis

A detailed assessment of the methods of analysis for fluazinam and the end-use product Allegro 500F Agricultural Fungicide is presented in Regulatory Note REG2003-12, *Fluazinam*.

3.0 Impact on Human and Animal Health

The toxicology data that were required as a condition of registration of fluazinam and Allegro 500F Agricultural Fungicide (see REG2003-12, *Fluazinam*) have been addressed. The review of these studies and the resulting changes to the toxicological database are summarized below.

3.1 Toxicology Summary

In acute and subchronic neurotoxicity studies in rats, treatment with fluazinam resulted in marked neuropathology in the form of vacuolation of the white matter of the brain. Special studies have been submitted that show this effect is not due to fluazinam itself, but rather to a manufacturing impurity. In the subchronic study, generalized toxicity was observed as decreased body weight and food efficiency. Dams in a developmental neurotoxicity study exhibited decreased body-weight gain and food consumption, while their offspring displayed decreased body weight and body-weight gain, increased time to sexual maturation, decreased activity and rearing counts, decreased surface righting reflex and increased fecal counts. There was no evidence of neurotoxicity in this study. (Appendix I, Table 1)

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account potential prenatal and postnatal toxicity and completeness of the data with respect to the exposure of and toxicity to infants and children. A different factor may be determined to be appropriate on the basis of reliable scientific data.

3.2 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for fluazinam is 0.0037 mg/kg bw/day. The chronic toxicity and oncogenicity study in mice was considered the most appropriate study to assess chronic dietary exposure. The no observed adverse effect level (NOAEL) was 1.1 mg/kg bw/day, based on increased incidences of brown pigmented macrophages in the liver, increased incidences of eosinophilic vacuolated hepatocytes in males and increased liver weights relative to body weights. The standard uncertainty factor (UF) of 100-fold is applied to account for intraspecies and interspecies variability. In light of the submission and review of the developmental neurotoxicity, the 10-fold factor required by the *Pest Control Products Act* has been reduced to 3-fold. A three-fold factor was retained to account for the endocrine-related toxicity noted in the database. This provides margins of safety of 2730 to the no observed effect

level (NOEL) for white matter vacuolation and 1900 to the NOEL for developmental effects in the rabbit developmental study.

The acceptable daily intake is calculated according to the following formula:

$$ADI = \frac{NOAEL}{UF} = \frac{1.1 \text{ mg/kg bw/day}}{300} = 0.0037 \text{ mg/kg bw/day}$$

A lifetime cancer risk (Q_1^*) had been assessed for fluazinam in the past based on a lack of mode of action data, but the applicant has since supplied such data. The PMRA has found no evidence suggesting that tumourigenesis follows a linear dose-response.

3.3 Determination of Acute Reference Dose

The recommended acute reference dose (ARfD) for fluazinam (general population) is 0.013 mg/kg bw. The most appropriate study for selection of a toxicity endpoint for acute dietary exposure was the rabbit developmental study, with a NOAEL of 4 mg/kg bw/day, based on decreased food consumption and liver histopathology at 7 mg/kg bw/day. The standard uncertainty factor of 100-fold is applied to account for intraspecies and interspecies variability and an additional 3-fold *Pest Control Products Act* factor is retained to protect for sensitivity of the young.

$$\text{ARfD (general population)} = \frac{NOAEL}{UF} = \frac{4 \text{ mg/kg bw}}{300} = 0.013 \text{ mg/kg bw}$$

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure is characterized as short-term or intermediate and is predominately by the dermal route. There was a 21-day repeat dose dermal toxicity study available; however, it does not account for the treatment-related histopathological and reproductive endpoints noted in rats and rabbits following 90-day and 1-year dietary administration. The rabbit developmental study with a NOAEL of 4 mg/kg bw/day was used for short-term exposure scenarios and the rat two-generation reproduction study with a NOAEL of 1.9 mg/kg bw/day was used for intermediate-term exposure scenarios. A target margin of exposure (MOE) of 100 was chosen based on intraspecies and interspecies differences.

Long-term studies in both rats and mice provided some evidence of treatment-induced oncogenicity of the thyroid (follicular cell adenomas and adenocarcinomas) and the liver (hepatocellular adenomas and carcinomas). Following an extensive internal review, the PMRA has found no evidence suggesting that tumourigenesis follows a linear dose-response. These tumour types are frequently seen in the respective rodents studied, but rarely in the general human population. An MOE approach is protective for potential tumourigenesis in humans.

Dermal Absorption
As the short-term and intermediate-term NOAELs are based on oral toxicology studies, systemic exposure was calculated from dermal deposition estimates using a 9% dermal absorption value. Details are presented in Regulatory Note REG2003-12, *Fluazinam*.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Handler Exposure and Risk

Risk estimates for workers mixing, loading and applying Allegro 500F Agricultural Fungicide are presented in Regulatory Note REG2003-12, *Fluazinam*, and are considered to be acceptable.

3.4.2.2 Postapplication Exposure and Risk

Risk estimates for workers entering potato fields treated with Agricultural Fungicide are presented in Regulatory Note REG2003-12, *Fluazinam*, and are considered to be acceptable.

3.4.3 Residential Exposure and Risk

3.4.3.1 Handler Exposure and Risk

There are no domestic class products; therefore, a residential handler assessment was not required.

3.4.3.2 Postapplication Exposure and Risk

There are no domestic class products; therefore, a residential postapplication assessment was not required.

3.4.4 Bystander Exposure and Risk Assessment

For bystanders, exposure is expected to be negligible, based on label directions intended to minimize spray drift.

3.5 Food Residues Exposure Assessment

No new residue chemistry data was submitted for the conversion to full registration.

3.5.1 Residues in Plant and Animal Foodstuffs

A detailed assessment of the residue chemistry database for fluazinam and the end-use product Allegro 500F Agricultural Fungicide are presented in Regulatory Note REG2003-12, *Fluazinam*.

3.5.2 Dietary Risk Assessment

The dietary risk assessment has been revised to reflect the results of submitted mechanistic and developmental neurotoxicity studies. Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates resulting from the use of fluazinam on potatoes in Canada as well as from importing treated peanuts into Canada. The assessment used the maximum residues limits and assumed 100% crop treated. The toxicological endpoints have been revised to reflect the removal of uncertainty factors that were applied due to the lack of the developmental neurotoxicity study.

Chronic dietary exposures for the representative population subgroups ranged from 0.8% to 1.9% of the ADI (0.0037 mg/kg bw/day) from all supported fluazinam food uses (food and water). The analysis indicated that dietary risk estimates were below the level of concern (100% of the ADI) for the general population and all population subgroups. The acute dietary exposure for females 13–49 years old (ARfD = 0.02 mg/kg bw) was estimated at 3.7% and 6.1% for the total population (ARfD = 0.013 mg/kg bw) from all supported fluazinam food uses (food and water). The current use of fluazinam encompasses only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered. The mechanistic data provided indicated that there was a threshold response, whereby low doses of fluazinam would result in a negligible cancer risk. As a result, the lifetime cancer risk (Q_1*) value was no longer required to calculate a lifetime risk. Therefore, a dietary cancer risk assessment was not conducted.

3.5.3 Aggregate Exposure and Risk

Acute and chronic aggregate exposures of fluazinam were considered acceptable and did not exceed the level of concern.

3.5.4 Maximum Residue Limits

MRLs (ppm)	Foods
0.02	Potato

No new MRLs are being established for the conversion to full registration.

The acute and chronic dietary risk estimates are summarized in Appendix I, Table 3.

4.0 Impact on the Environment

Details of the environmental fate and environmental toxicology assessment in Regulatory Note REG2003-12, *Fluazinam*, remain unchanged. Assessment of the additional data provided by the registrant and the risk associated with the end-use product are summarized below.

4.1 Fate and Behaviour in the Environment

During the initial review, insufficient information was identified for the assessment of the Toxic Substances Management Policy (TSMP) Track 1 implications of the major hydrolysis transformation product 5-chloro-6-[3-chloro-2, 6-dinitro-4-trifluoromethylanilino) nicotinic acid (CAPA), which reached maximum concentrations on day 28 (test termination of the hydrolysis study). Two studies were submitted to the PMRA for the conversion of fluazinam from conditional registration to full registration, a hydrolysis and a log K_{ow} study. CAPA was found to be stable to hydrolysis at pHs 7 and 9. The first order half-life of CAPA was calculated to be 198.0 and 106.6 days at pH 7 and pH 9, respectively. The hydrolysis of CAPA was not studied at pH 5.0 as hydrolysis of fluazinam leads to the formation of CAPA only under neutral to basic conditions. The log K_{ow} of CAPA was shown to be 1.76 at 25° ± 1°C. CAPA is, thus, not expected to bioaccumulate. Data are summarized in Appendix I, Table 4.

4.2 Environmental Toxicology

In the previous review of fluazinam (REG2003-12), fluazinam was shown to partition into sediment and rapidly transform into the major transformation product SDS-67200 under anaerobic sediment-water conditions. The toxicity of SDS-67200 towards sediment dwelling species was not known. In response to this concern, the applicant submitted two acute toxicity studies of sediment dwelling species, *Chironomus tentans* and the freshwater amphipod *Hyalella azteca*. The no observed effect concentration (NOEC) and lowest observed effect concentration (LOEC) of SDS-67200 to *Chironomus tentans* and *Hyalella aztech* were estimated to be 4.7 mg/kg and greater than 12.0 mg/kg, and 0.14 mg/kg and 0.67 mg/kg, respectively.

4.3 Risk Characterization

4.3.1 Risk to Aquatic Organisms

Two sediment dwelling acute toxicity studies were submitted for the conversion of fluazinam from conditional registration to full registration. These studies were conducted with the anaerobic aquatic transformation product SDS-67200. The toxicity endpoints for these acute studies on *Chironomus tentans* and *Hyalella azteca* were used to calculate the risk of the SDS-67200 to sediment dwelling organisms. The following endpoints were used for these organisms:

Chironomus tentans: $LC_{50} > 12.0$ mg a.i./kg
Hyalella azteca: $LC_{50} > 4.6$ mg a.i./kg

The screening level RQs calculated for both *Chironomus tentans* and *Hyalella azteca* indicate that SDS-67200 presents negligible risk to sediment dwelling organisms.

5.0 Value

Details of the value and efficacy assessment of Allegro 500F Agricultural Fungicide are presented in Regulatory Note REG2003-12, *Fluazinam*.

6.0 Toxic Substances Management Policy Considerations

During the original review of Technical Fluazinam Fungicide and Allegro 500F Agricultural Fungicide, the PMRA had taken into account the federal Toxic Substances Management Policy and its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. It was determined that this product did not meet the TSMP Track 1 criteria. This product was also found not to contain any impurities of human health or environmental concerns and did not contain any USEPA or PMRA List 1 or 2 formulants.

Studies submitted for the major hydrolysis transformation product CAPA showed , although its value for half-life in water (198 days at pH 7) meets the TSMP Track 1 cut-off criteria for water (>182 days), the log K_{ow} of 1.76, is below the TSMP Track 1 cut-off criterion of $\geq$ 5.0. CAPA does not meet all Track 1 criteria. Therefore, it is not classified as a Track 1 substance.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted is adequate to define the majority of toxic effects that may result from human exposure to fluazinam.

Fluazinam caused thyroid tumours in male rats and liver tumours in male mice, but was not genotoxic. Mode of action data was submitted that supported a threshold dose response. There was also no indication that fluazinam caused damage to the nervous system. The first signs of toxicity in animals given daily doses of fluazinam over longer periods of time were effects on body weight, liver, uterus and blood chemistry. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When fluazinam was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, though the effects observed were more severe indicating that the fetus was more sensitive to fluazinam than the adult animal. Also, some potentially endocrine-related effects were seen in the two year mouse study. Consequently, extra safety factors were applied during the risk assessment to further reduce the allowable level of human exposure to fluazinam.

The residue database is complete. The nature of the residue in potatoes and livestock is adequately understood. The residue definition is fluazinam for root crops and rotational crops. The residue definition is fluazinam 4-chloro-N^2-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-nitro-5-(trifluoromethyl)-1,2-benzenediamine (AMPA) and 3-chloro-2-(2,6-diamino-3-chloro-α,α,α-trifluoro-p-toluidino)-5-(trifluoromethyl) pyridine (DAPA) in animal matrices. Dietary risks from food and water are not of concern. The use of fluazinam on potatoes does not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed, and a maximum residue limit on potatoes to protect human health is 0.02 ppm.

Mixers, loaders, applicators and workers entering treated areas are not expected to be exposed to levels of Fluazinam that will result in unacceptable risk when Allegro 500F Agricultural Fungicide is used according to label directions.

7.2 Environmental Risk

The level of concern is exceeded for several non-target organisms at the proposed rate of use of fluazinam. To protect sensitive aquatic habitats, buffer zones were included to mitigate the risks. Environmental hazard statements were added to the label for the protection of sensitive terrestrial and aquatic species.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of Technical Fluazinam Fungicide and Allegro 500F Agricultural Fungicide to control late blight on potatoes. An evaluation of current scientific data from the applicant has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
AMPA	4-chloro-N^2-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-nitro-5-(trifluoromethyl)-1,2-benzenediamine
ARfD	acute reference dose
bw	body weight
bwg	body-weight gain
CAPA	5-chloro-6-[3-chloro-2, 6-dinitro-4-trifluoromethylanilino) nicotinic acid
CAS	chemical abstracts service
cm	centimetres
DAPA	3-chloro-2-(2,6-diamino-3-chloro-α, α, α-trifluoro-p-toluidino)-5-(trifluoromethyl) pyridine
EEC	estimated environmental concentration
g	gram
GLP	good laboratory practice
ha	hectare(s)
HPLC	high performance liquid chromatography
HYPA	5-[(3-chloro-5-(trifluoromethyl)-2-pyridyl)amino]-α, α, α-trifluoro-4,6-dinitro-o-cresol
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
MAPA	3-chloro-N^1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-6-nitro-4-(trifluoromethyl)-1,2-benzenediamine
MAS	maximum average score
mg	milligram
mL	millilitre
MOE	margin of exposure
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
Q_1^*	lifetime cancer risk
RQ	risk quotient

SDS-67200	2-chloro-6-[(3-chloro-5-(trifluoromethyl)-2-pyridyl)-α, α, α-trifluoro-5-nitro-*m*-cresol
$t_{1/2}$	half-life
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency

Appendix I Tables and Figures

Table 1 Neurotoxicity

Study	Test Species/Strain and Doses	NOAEL and LOAEL (mg/kg bw/day)	Target organ/ Significant Effects/ Comments	Reference
Developmental	97.8%, Crl:CD (SD) IGS BR rats, 0, 2, 10, 50 mg/kg bw/day, 24 females/dose	Maternal NOAEL 2 mg/kg bw/day Maternal LOAEL 10 mg/kg bw/day Offspring NOAEL 2 mg/kg bw/day Offspring NOAEL 10 mg/kg bw/day	Maternal Offspring <u>10 mg/kg/d and above</u> ↓ bw, bwg ↑ time to sexual maturation ↓ surface righting reflex ♀ ↓ activity, rearing counts ↓ fecal counts ♂ <u>50 mg/kg/d</u> Dark and/or large abdomen Prominent perigenital regions ♀ ↓ Pupil contraction reflex ↓ Peak amplitude without pre-pulse ♂	1154858

Table 2 Revised Toxicology Endpoints for Use in Health Risk Assessment

Recommended ARfD	0.013 mg/kg bw based on rabbit developmental study (4 mg/kg bw/day with 100-fold uncertainty factor and threefold safety factor to protect for sensitivity of the young).
Recommended ADI	0.0037 mg/kg bw/day based on 2-year carcinogenicity in mice (1.1 mg/kg bw/day with 100-fold uncertainty factor and three-fold safety factor for potential endocrine-related effects (testicular atrophy, pancreatic exocrine atrophy ♀).

Table 3 Overview of Risk Assessment

DIETARY RISK from food and water			
Chronic Non-Cancer Dietary Risk **ADI = 0.0037 mg/kg bw/day** **EEC = 0.00077 mg/kg (Level II, chronic)**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (MRLs)	**Food + EEC**
	All infants < 1 yr old	0.4	1.9
	Children 1 to 2 yrs	1.3	1.9
	Children 3 to 5 yrs	1.2	1.8
	Children 6 to 12 yrs	0.8	1.2
	Youth 13 to 19 yrs	0.6	0.9
	Adults 20 to 49 yrs	0.5	0.9
	Adults 50+ yrs	0.4	0.9

	Females 13 to 49 yrs	0.4	0.8
	Total Population	0.6	1
Acute Dietary Exposure Analysis Deterministic, 95th percentile EEC = 0.01455 (level II, Acute)	**POPULATION**	**ESTIMATED RISK (% of ARfD)**	
		Food (MRLs)	**Food + EEC**
ARfD = 0.02 mg/kg bw	**Females 13 to 49 yrs**	0.33	3.67
ARfD = 0.013 mg/kg bw	**Total Population**	0.63	6.12

Table 4 Mobility of HYPA and CAPA

Compound	Fate process	Endpoint	Interpretation[a]	Reference
HYPA	Adsorption/ desorption	Adsorption K_{oc}: 450 to 1667 mL/g	Low to moderate mobility in soil, and some potential for partitioning into sediment.	1154859 1154857
CAPA	Adsorption/ desorption	Adsorption K_{oc}: 1289 to 3784 mL/g	Slight to low mobility in soil, and a potential for partitioning into sediment.	

[a] Classification of adsorption/desorption and mobility according to McCall et al.[5]

[5] McCall, J.P., D.A. Laskowski, R.L. Swann and H.J. Dishburger. 1981. Measurement of Sorption Coefficients of Organic Chemicals and Their Use in Environmental Fate Analysis. In: Proceedings of Symposium, Test protocols for environmental fate and movement of toxicants, Association of Official Environmental Chemists, 94th Annual Meeting, Washington, DC, October 21–22, 1980, pp. 89–109.

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

1.0 Chemistry

PMRA #	Reference
1154857	2004, Determination of n-Octanol/Water Partition Coefficient - CAPA, Ricerca 017119-1, DACO: 2.14.1
11243579	1999, Fluazinam (IKF - 1216) - Method Validation [Determination of AI and Related Impurities in Fluazinam (IKF-1216), TGAI by HPLC, Analytical Services, 4039-98-0203-AS-001, DACO: 2.13.1
1260870	Product Chemistry - Fluazinam - Applicant, Manufacturer and Manufacturing Plant Name and Address, DACO: 2.1,2.2
1260871	2005, Description of Beginning Materials and Manufacturing Process Technical Fluazinam (IKF-1216) as Modified - Yokkaichi Plant, Ishihara Sangyo Kaisha, Ltd., 216-04-06102-1, DACO: 2.11.1,2.11.2,2.11.3
1260872	2000, Description of Beginning Materials and Manufacturing Process Technical Fluazinam (IKF-1216) as Modified, Ishihara Sangyo Kaisha, Ltd., 216-00-06102-3, DACO: 2.11.1,2.11.2,2.11.3
1260873	2005, Discussion of Formation of Impurities Technical Fluazinam (IKF-1216) from Modified Process - Yokkaichi Plant, Ishihara Sangyo Kaisha, Ltd., 216-04-06103-1, DACO: 2.11.4
1260874	2005, Product Identity and Composition / Technical Fluazinam (IKF-1216) from Modified Process - Yokkaichi Plant, Ishihara Sangyo Kaisha, Ltd., 216-04-06101-1, DACO: 2.13.2
1260875	2004, Fluazinam Technical, Analysis of Five Batches (Sample Group 1), Midwest Research Institute, 310260.1.029, DACO: 2.13.3
1260876	2000, Fluazinam: Analysis of Twenty (20) Batches from Manufacturing Site in France (SISSA) Using Modified Process, Certified Limits, Ishihara Sangyo Kaisha, Ltd, 216-00-06202-1, DACO: 2.13.3
1260877	2000, Product Identity and Composition / Technical Fluazinam (IKF-1216) from Modified Process, Ishihara Sangyo Kaisha, Ltd., 216-00-06101-3, DACO: 2.13.2
1260878	2000, Discussion of Formation of Impurities Technical Fluazinam (IKF-1216) from Modified Process, Ishihara Sangyo Kaisha, Ltd., 216-00-06103-3, DACO: 2.11.4

1260879 2004, Certified Limits Technical Fluazinam (IKF-1216) from Modified Process - Yokkaichi Plant, Ishihara Sangyo Kaisha, Ltd., 216-04-06202-1, DACO: 2.12.1

1260880 2000, Certified Limits Technical Fluazinam (IKF-1216) from Modified Process, Ishihara Sangyo Kaisha, Ltd., 216-00-06202-1, DACO: 2.12.1

2.0 Impact on Human and Animal Health

PMRA # Reference

1154858 2005, Technical Fluazinam: Developmental Neurotoxicity Study in the Rat by Oral (Gavage) Administration., ISK 272/042019, DACO: 4.5.14

3.0 Impact on the Evironment

PMRA # Reference

1154857 2004. Determination of *n*-octanol/water partition coefficient - CAPA. Study No. IB-2004-JLW-003-01-00. Document No. 017119-1.

1154859 2004. A hydrolysis study of [^{14}C]CAPA in water. Document No. 017120-1.

1154860 2006. SDS-67200 - Toxicity to midge (*Chironomus tentans*) during a 10-day sediment exposure. Study No. 13562.6135

1154861 2006. SDS-67200 - Toxicity to freshwater amphipods (*Hyalella azteca*) during a 10-day sediment exposure. Study No. 13562.6136.